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PATENT
Attorney Docket 056365-5049

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

In re Application of: **Gordon Ng *et al.***

Application No. **08/670,119**

Filed: **June 25, 1996**

Group Art Unit: **1647**

Examiner: **Jason Galvez**

For: **Receptor and Transporter Antagonists**

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TRANSMITTAL FORM

1. Further to the Notice of Appeal filed on November 5, 2004, transmitted herewith is Appellants' Brief Under 37 C.F.R. 1.192.
2. Additional Papers Submitted:
 - (i) Copy of Supplemental Response and Amendment under 37 C.F.R. 1.116 filed on March 7, 2005.
 - (ii) Copy of return receipt postcard dated March 7, 2005.
3. Extension of Time: The proceedings herein are for a patent application and the provisions of 37 C.F.R. § 1.136(a) apply. Appellants petition for an additional three month extension of time further extending the period of response from March 5, 2005 to June 5, 2005. This response is being filed under the next business day rule on Monday, June 6, 2005, as the due date for the filing of the Appeal Brief fell on a Sunday (June 5, 2005). If Applicants have inadvertently overlooked the need for an additional extension of time, please consider this a petition therefore. The Commissioner is hereby authorized to charge any additional fees which may be required, including fees due under 37 C.F.R. § 1.16 and § 1.17, or credit any overpayment to Deposit Account 50-0310.
4. Fee Payment: The Commissioner is hereby authorized to charge **\$1,105.00** to Deposit Account No. 50-0310 for payment of the fee for filing a brief in support of an appeal (\$250.00) and the additional three month extension of time fee (\$855.00), all fees at the small entity rate.
5. Constructive Petition: **Except** for issue fees payable under 37 C.F.R. § 1.18, the Commissioner is hereby authorized by this paper to charge any additional fees during the entire pendency of this application including fees due under 37 C.F.R. § 1.16 and § 1.17 which may be required, including any required extension of time fees, or credit any overpayment to Deposit Account 50-0310. This

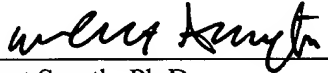
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paragraph is intended to be a **constructive petition for extension of time** in accordance with 37 C.F.R. § 1.136(a)(3).

Dated: **June 6, 2005**
Morgan, Lewis & Bockius LLP
Customer No. **09629**
1111 Pennsylvania Avenue, N.W.
Washington, D.C. 20004
202-739-3000

Respectfully submitted,
Morgan, Lewis & Bockius LLP


Robert Smyth, Ph.D.
Registration No. 50,801



PATENT
Attorney Docket 56365-5049

**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES**

In re Application of: **Gordon Ng *et al.***

Application No. **08/670,119**

Filed: **June 25, 1996**

Group Art Unit: **1647**

Examiner: **Jason Galvez**

For: **Receptor and Transporter Antagonists**

APPELLANTS' BRIEF UNDER 37 C.F.R. 1.192

This brief is in furtherance of the Notice of Appeal filed on November 5, 2005. The fees required under 37 C.F.R. 41.20(b)(2) are being filed concurrently herewith.

1. The Real Party in Interest

The real parties in interest in this appeal is Gordon Ng, Philip Seeman, Brian F. O'Dowd and Susan George.

2. Related Appeals and Interferences

None.

3. Status of Claims in Application

Claims 67 to 78 and 80 to 86 are pending in the application. No claims have been allowed. Claims 67 to 78 and 81 to 86 have been finally rejected and are on appeal. Claims 67 to 78 and 80 to 86 have been rejected under 35 U.S.C. 112 (first paragraph).

4. Status of Amendments

A Response and Amendment under 37 C.F.R. 1.116 was filed on November 3, 2004 after the final Office Action dated May 6, 2004. The rejection of claim 80 under 35 U.S.C. 112 (first paragraph) was withdrawn while the rejection of claims 67 to 78 and 81 to 86 under 35 U.S.C. 112 (first paragraph) and the objection to claim 80 were maintained in an Advisory Action dated

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February 2, 2005. A second Response and Amendment under 37 C.F.R. 1.116 was filed on March 7, 2005. The Examiner has not yet issued an advisory action or notice of allowance in response to this second Response and Amendment. Appellants hereby request entry of the second Response and Amendment under 37 C.F.R. 1.116 previously filed on March 7, 2005 as it puts that application in better condition for appeal (see attached copy).

5. Summary of Claimed Subject Matter

Appellant's invention relates to the field of integral membrane proteins which act as receptors or signal transducers. More specifically, it relates to the identification and preparation of specific antagonists of the function of such proteins.

6. Issues to be Reviewed on Appeal

Whether claims 67 to 78 and 81 to 86 as amended are unpatentable under 35 U.S.C. 112 (first paragraph) as being based on a nonenabling and unsupportive specification.

In the Final Office Action dated May 6, 2004, the claims were rejected as failing to comply with the enablement requirement and the written description requirement under 35 U.S.C. 112 (first paragraph).

In support of her rejection based upon lack of enablement, the Examiner alleged that claims 67 to 78 and 81 to 86 contain subject matter which was not described in the invention in such a way as to reasonably convey to one skilled in the art that the inventors, at the time the application was filed, had possession of the claimed invention. The Examiner contends that claims 67 to 78 and 81 to 86 are drawn to peptides comprising at least nine contiguous amino acid residues from a transmembrane domain of an alpha-1A adrenergic receptor and that there are no examples of antagonists peptides nine amino acid residues in length (see Final Office Action dated May 6, 2004 at page 2, last paragraph through page 3, first paragraph).

In support of her rejection of claims 67 to 78 and 81 to 86 based upon lack of written description, the Examiner alleged that the specification has not described the genus in such a way that one of skill in the art would be able to identify effective antagonist peptides (see Advisory Office Action dated February 2, 2005).

7. Argument

i. The Examiner has improperly found lack of enablement

Appellants submit that the specification provides sufficient enablement for the amended claims. Specifically, the amended claims require administration of peptides containing at least sixteen contiguous peptides from a transmembrane domain of the alpha-1A adrenergic receptor for the treatment of hypertension. Appellants note and emphasize that the specification discloses *in vivo* experimental data for inhibition of drug-induced increases in blood pressure (*i.e.*, hypertension) associated with alpha-1A adrenergic receptor activity (see, for example, page 42, line 32 to page 43, line 30) following administration of peptides derived from the transmembrane domains of this receptor of about sixteen amino acids residues in length (see Figure 6c). Finally, the Examiner previously indicated that the specification was enabling for the claimed peptide sequences that are antagonists to D1 or D2 dopamine receptors, or beta-1 or alpha-1A adrenergic receptors (see Office Action dated August 13, 2003 at page 4).

With regard to amended claim 68 relating to conservative amino acid substitutions in the sixteen contiguous amino acids selected from a transmembrane domain, the Examiner indicated that the specification provides no guidance as to which amino acid residues in the transmembrane sequence can be changed to yield a functional equivalent. Appellants note and emphasize the examples of conservative amino acid substitutions disclosed in the specification (see page 14, lines 3 to 10). Given this disclosure in the specification, Appellants submit that the skilled artisan could readily determine which conservative substitutions are encompassed in amended claim 68 to practice the invention without undue experimentation.

ii. The Examiner has improperly found lack of written support

Appellants submit that the substitute claims meet the written description provision of 35 U.S.C. 112 (first paragraph) because the specification provides multiple examples of peptides derived from the transmembrane domains of the G protein-coupled receptors (*i.e.*, alpha-1A adrenergic receptor) that are effective for modulating G protein receptor activity (see, for example, experimental data relating to the D2 Dopamine Receptor in Example 1 on page 31). Furthermore, the Examiner previously acknowledged that the specification provides sufficient written description for a method of treating a disorder for which administration of a specific

antagonist of either the D2 dopamine receptor, beta-1 adrenergic receptor or an alpha-1A adrenergic receptor is effective (see Office Action dated August 13, 2003 at page 9).

With regard to conservative substitutions in the sixteen contiguous amino acids as set forth in amended claim 68, Appellants note and emphasize that the specification sets forth that a peptide containing a conservative amino acid substitution must retain activity (see page 13, lines 6 to 12). Furthermore, Appellants submit that the comments relating to the Townsend-Nicholson *et al.* are not applicable to the amended claims because a mutation which alters activity cannot, by definition, be a conservative substitution. The situation where a single amino acid substitution eliminates the activity of a protein is generally an exception to the rule rather than the more common situation where multiple conservative substitutions can be made without affecting protein function.

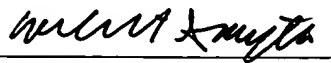
8. Conclusion

As shown by the preceding arguments, claims 67 to 78 and 81 to 86 are patentable under 35 U.S.C. 112 (first paragraph). Appellants respectfully request reversal of the rejections under 35 U.S.C. 112 (first paragraph) and allowance of pending claims 67 to 78 and 80 to 86.

Except for issue fees payable under 37 C.F.R. 1.18, the Commissioner is hereby authorized by this paper to charge any additional fees during the entire pendency of this application including fees due under 37 C.F.R. 1.16 and 1.17 which may be required, including any required extension of time fees, or credit any overpayment to Deposit Account 50-0310. This paragraph is intended to be a constructive petition for extension of time in accordance with 37 C.F.R. 1.136(a)(3).

Dated: **June 6, 2005**
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Respectfully submitted
Morgan, Lewis & Bockius LLP


Robert Smyth
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Claims Appendix

Claims 1 to 66. (cancelled)

67. A method of treating hypertension in a mammal in need of said treatment comprising administering an effective amount of a peptide comprising at least nine contiguous amino acids residues selected from an amino acid sequence of a transmembrane domain of an alpha-1A adrenergic receptor selected from the group consisting of:

GVGVGVFLAAFILMAVAGNLLVILSV (SEQ ID NO: 23);
FIVNLAVADLLLSATVLPFSATMEVL (SEQ ID NO: 24);
DVWAAVDVLCCTASILSLCTISV (SEQ ID NO: 25);
AAILALLWVVALVVS VGPLL GWKEP (SEQ ID NO: 26);
AGYAVFSSVCSFYLPMAVIVVMYC (SEQ ID NO: 27);
LAIVVG VFVLCWF PFFFV LPLGSL (SEQ ID NO: 28); and
EGVFKVIFWLGYFN SCVNPLIYPCS (SEQ ID NO: 29).

68. A method of treating hypertension in a mammal in need of said treatment comprising administering an effective amount of a peptide comprising at least nine contiguous amino acids selected from an amino acid sequence of a transmembrane domain of an alpha-1A adrenergic receptor selected from the group consisting of:

GVGVGVFLAAFILMAVAGNLLVILSV (SEQ ID NO: 23);
FIVNLAVADLLLSATVLPFSATMEVL (SEQ ID NO: 24);
DVWAAVDVLCCTASILSLCTISV (SEQ ID NO: 25);
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LAIVVG VFVLCWF PFFFV LPLGSL (SEQ ID NO: 28); and
EGVFKVIFWLGYFN SCVNPLIYPCS (SEQ ID NO: 29),

wherein the peptide contains one or more conservative amino acid substitutions in the nine contiguous amino acids.

69. The method according to claim 67 or 68 wherein the peptide binds to a transmembrane domain of the alpha-1A adrenergic receptor.

70. The method according to claim 69 wherein the peptide inhibits the activity of the alpha-1A adrenergic receptor.

71. The method according to claim 70 wherein the inhibition of the activity of the alpha-1A adrenergic receptor induces vasodilation or inhibits vasoconstriction.

72. The method according to claim 67 or 68 wherein the peptide retains a helical confirmation.

73. The method according to claim 67 or 68 wherein the peptide comprises up to twenty-six amino acid residues.

74. The method according to claim 67 or 68 wherein one or more of the amino acid residues of the peptide contains a side chain modification.

75. The method according to claim 67 or 68 wherein one or more of the amino acid residues of the peptide is a non-natural amino acid.

76. The method of claim 67 or 68 wherein the peptide is altered to increase plasma half-life following administration.

77. The method of claim 76 wherein the peptide is conjugated to one or more water-soluble polymers.

78. The method of claim 76 wherein the peptide is incorporated into a polymeric matrix.

Claim 79 (cancelled).

80. The method according to claim 67 wherein the amino acid sequence of the peptide is selected from the group consisting of:

VFKVIFWLGYFNSCVN (SEQ ID NO: 31).

81. The method according to claim 67 or 68 wherein the mammal is a human.

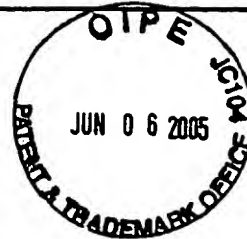
82. The method according to claim 67 or 68 where in the peptide is administered in combination with a pharmaceutically acceptable carrier.

83. The method according to claim 82 wherein the pharmaceutically acceptable carrier enhances stability of the peptide.

84. The method according to claim 82 wherein the pharmaceutically acceptable carrier enhances adsorption of the peptide.

85. The method according to claim 67 or 68 wherein the peptide is administered by a route selected from the group consisting of oral, nasal, buccal, intravenous, intramuscular, subcutaneous and transdermal.

86. A method of treating hypertension in a human in need of said treatment consisting essentially of administering an effective amount of a peptide comprising at least nine contiguous amino acids residues selected from an amino acid sequence of a transmembrane domain of an alpha-1A adrenergic receptor.



PLEASE STAMP AND RETURN TO SHOW RECEIPT OF:

In re Application of: Gordon Ng *et al.*
Application No. 08/670,119
Filed: June 25, 1996
Group Art Unit: 1647
Examiner: Rachel Kapust
For: Receptor and Transporter Antagonists

Attention: Mail Stop AF

Papers Submitted:

1. Transmittal
2. Supplemental Response and Amendment Under 37 C.F.R. 1.116
3. Authorization to charge deposit account - \$225.00

Date: March 7, 2005
Attorney Docket 056365-5049
RJS:ghb





PATENT
Attorney Docket 056365-5049

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of: **Gordon Ng *et al.***

Application No. **08/670,119**

Filed: **June 25, 1996**

Examiner: **Rachel Kapust**

Group Art Unit: **1647**

For: **Receptor and Transporter Antagonists**

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TRANSMITTAL FORM

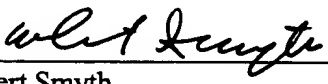
1. Supplemental to the Response and Amendment Under 37 C.F.R. 1.116 filed on November 3, 2004 and the Notice of Appeal filed on November 5, 2004, transmitted herewith is a Supplemental Response and Amendment Under 37 C.F.R. 1.116 in response to the Final Office Action dated May 6, 2004.
2. Extension of Time: The proceedings herein are for a patent application and the provisions of 37 C.F.R. 1.136(a) apply. Further to the Notice of Appeal submitted on November 5, 2004, Applicants petition for a two-month extension of time from January 5, 2005 to March 5, 2005, the fee for a small entity which is **\$225.00** as set out in 37 C.F.R. 1.17(a). The Commissioner is hereby authorized to charge any additional fees which may be required, including fees due under 37 C.F.R. 1.16 and 1.17, or credit any overpayment to Deposit Account 50-0310. This request is being filed under the next business day rule on Monday, March 7, 2005 as the due date for responding fell on a Saturday (March 5, 2005).
4. Fee Calculation (37 C.F.R. 1.16):

CLAIMS AS AMENDED						
	Remaining		Previously Paid	Extra	Rate	Total Fees
Total Claims	34	minus	59	0	\$50.00 each=	0.00
Independent Claims	3	minus	3	0	\$200.00 each=	0.00
First presentation of Multiple dependent claim					\$360.00	0.00
SUB-TOTAL =						0.00
Reduction by ½ for filing by a small entity						
TOTAL FEE =						0.00

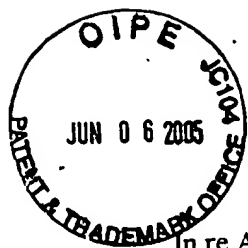
5. **Fee Payment:** The Commission is hereby authorized to charge **\$225.00** to Deposit Account 50-0310 for payment of the two-month extension of time fee at the small entity rate.
6. **Constructive Petition:** **Except** for issue fees payable under 37 C.F.R. 1.18, the Commissioner is hereby authorized by this paper to charge any additional fees during the entire pendency of this application including fees due under 37 C.F.R. 1.16 and 1.17 which may be required, including any required extension of time fees, or credit any overpayment to Deposit Account 50-0310. This paragraph is intended to be a **constructive petition for extension of time** in accordance with 37 C.F.R. 1.136(a)(3).

Dated: **March 7, 2005**
Morgan, Lewis & Bockius LLP
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Robert Smyth
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PATENT
Attorney Docket 056365-5049

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of: **Gordon Ng *et al.***

Application No. **08/670,119**

Filed: **June 25, 1996**

Examiner: **Gary L. Kunz**

Group Art Unit: **1647**

For: **Receptor and Transporter Antagonists**

SUPPLEMENTAL RESPONSE AND AMENDMENT UNDER 37 C.F.R. 1.116

Further in response to the Final Office Action dated May 6, 2004, the period for response having been extended from January 5, 2005 to March 5, 2005 by payment of an additional two-month extension of time, please amend the above-referenced application as follows:

Amendments to the Claims begin on page 2 of this paper.

Remarks begin on page 5 of this paper.

Amendments to the Claims:

Please cancel claim 79 without prejudice or disclaimer.

Please amend claims 67, 68 and 80 as follows:

This listing of claims will replace all prior versions and listing of claims in the application.

Listing of Claims:

Claims 1 to 66. (cancelled)

67. (currently amended) A method of treating hypertension in a mammal in need of said treatment comprising administering an effective amount of a peptide comprising at least ~~nine~~ sixteen (16) contiguous amino acids residues selected from an amino acid sequence of a transmembrane domain of an alpha-1A adrenergic receptor selected from the group consisting of:

GVGVGVFLAAFILMAVAGNLLVILSV (SEQ ID NO: 23);
FIVNLAVADLLLSATVLPFSATMEVL (SEQ ID NO: 24);
DVWAAVDVLCCTASILSLCTISV (SEQ ID NO: 25);
AAILALLWVVALVVS VGPLL GWKEP (SEQ ID NO: 26);
AGYAVFSSVCSFYLPMAVIVVMYC (SEQ ID NO: 27);
LAIVVGVFVLCWFPPFFVLPLGSL (SEQ ID NO: 28); and
EGVFKVIFWLGYFNSCVNPLIYPCS (SEQ ID NO: 29).

68. (currently amended) A method of treating hypertension in a mammal in need of said treatment comprising administering an effective amount of a peptide comprising at least ~~nine~~ sixteen (16) contiguous amino acids selected from an amino acid sequence of a transmembrane domain of an alpha-1A adrenergic receptor selected from the group consisting of:

GVGVGVFLAAFILMAVAGNLLVILSV (SEQ ID NO: 23);
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LAIVVGVFVLCWFPPFFVLPLGSL (SEQ ID NO: 28); and
EGVFKVIFWLGYFNSCVNPLIYPCS (SEQ ID NO: 29),

wherein the peptide contains one or more conservative amino acid substitutions in the nine contiguous amino acids.

69. (previously presented) The method according to claim 67 or 68 wherein the peptide binds to a transmembrane domain of the alpha-1A adrenergic receptor.

70. (previously presented) The method according to claim 69 wherein the peptide inhibits the activity of the alpha-1A adrenergic receptor.

71. (previously presented) The method according to claim 70 wherein the inhibition of the activity of the alpha-1A adrenergic receptor induces vasodilation or inhibits vasoconstriction.

72. (previously presented) The method according to claim 67 or 68 wherein the peptide retains a helical confirmation.

73. (previously presented) The method according to claim 67 or 68 wherein the peptide comprises up to twenty-six amino acid residues.

74. (previously presented) The method according to claim 67 or 68 wherein one or more of the amino acid residues of the peptide contains a side chain modification.

75. (previously presented) The method according to claim 67 or 68 wherein one or more of the amino acid residues of the peptide is a non-natural amino acid.

76. (previously presented) The method of claim 67 or 68 wherein the peptide is altered to increase plasma half-life following administration.

77. (previously presented) The method of claim 76 wherein the peptide is conjugated to one or more water-soluble polymers.

78. (previously presented) The method of claim 76 wherein the peptide is incorporated into a polymeric matrix.

Claim 79 (cancelled).

80. (currently amended) The method according to claim 67 wherein the amino acid sequence of the peptide is selected from the group consisting of:

VFKVIFWLGYFNSCVN (SEQ ID NO: 31) [~~and~~
~~VFKVIFWLGYFNS (SEQ ID NO: 32)]~~.

81. (previously presented) The method according to claim 67 or 68 wherein the mammal is a human.

82. (previously presented) The method according to claim 67 or 68 where in the peptide is administered in combination with a pharmaceutically acceptable carrier.

83. (previously presented) The method according to claim 82 wherein the pharmaceutically acceptable carrier enhances stability of the peptide.

84. (previously presented) The method according to claim 82 wherein the pharmaceutically acceptable carrier enhances adsorption of the peptide.

85. (previously presented) The method according to claim 67 or 68 wherein the peptide is administered by a route selected from the group consisting of oral, nasal, buccal, intravenous, intramuscular, subcutaneous and transdermal.

86. (previously presented) A method of treating hypertension in a human in need of said treatment consisting essentially of administering an effective amount of a peptide comprising at least nine contiguous amino acids residues selected from an amino acid sequence of a transmembrane domain of an alpha-1A adrenergic receptor.

Summary of the Advisory Office Action

1. The rejection of claim 80 under 35 U.S.C. 112 (first paragraph) was withdrawn.
2. The remaining rejections were maintained.

Summary of the Office Action

1. The previous rejection of claims 18, 20 to 37 and 60 to 65 under 35 U.S.C. 112 (first paragraph) as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter which the Applicants regard as the invention has been withdrawn.
2. The previous rejection of claims 18, 20 to 22, 36 and 60 to 61 under 35 U.S.C. 102(b) as allegedly being anticipated by *Lofts et al.* (1993) Oncogene 8, 2813-2820 has been withdrawn.
3. The previous rejection of claims 18, 20 to 24, 26, 28, 29, 36, 37, 60 and 61 under 35 U.S.C. 102(e) as allegedly being anticipated by *Murphy et al.* (1996) U.S. Patent 5,508,384 has been withdrawn.
4. Claims 67 to 78 and 81 to 86 were rejected under 35 U.S.C. 112 (first paragraph) as allegedly failing to comply with the written description requirement.
5. Claim 80 was rejected under 35 U.S.C. 112 (first paragraph) as allegedly failing to comply with the written description requirement.
6. Claim 79 was objected to as being dependent upon a rejected base claim but would be allowable if written in independent form including all of the limitations of the base claim and any intervening claims.

Response to the Office Action

The Advisory Office Action dated February 2, 2005 and the Office Action dated May 6, 2004 have been carefully reviewed and the following amendments and comments are made in response. In view of the above amendments and following remarks, Applicants respectfully request reconsideration and reexamination of this application and the timely allowance of the pending claims.

Rejections under 35 U.S.C. 112 (first paragraph)

Claims 67 to 78 and 81 to 86 were rejected under 35 U.S.C. 112 (first paragraph) as allegedly failing to comply with the written description requirement. Without acquiescing to the merits of the rejection, Applicants have amended claims 67 and 68 such that they incorporate all of the limitations of claim 79 and provide for a peptide that is at least sixteen amino acid residues in length. Applicants bring to the attention of the Examiner the experimental data disclosed on pages 42 to 43 where a peptide of

sixteen amino acids in length whose sequence was derived from the transmembrane domain of an alpha-1A adrenergic receptor.

Claim 80 was also rejected under 35 U.S.C. 112 (first paragraph) as allegedly failing to comply with the written description requirement. Without acquiescing to the merits of the rejection, this claim has been amended to remove the typographical error which resulted in the rejection.

Claims 67 to 78 and 81 to 86 were rejected under 35 U.S.C. 112 (first paragraph) for lack of enablement. Applicants have amended these claims so that they now provide for a peptide that is at least sixteen amino acid residues in length. In view of the *in vivo* experimental data disclosed in the specification and discussed above, Applicants submit that the specification adequately enables the amended claims. In view of the above amendments and remarks, Applicants respectfully request withdrawal of these rejections.

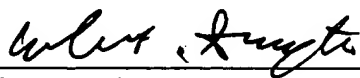
Conclusion

Applicants respectfully request reconsideration of the subject application in view of the substitute claims and the above remarks. It is respectfully submitted that this application is now in condition for allowance. Should the Examiner believe it to be useful, an interview with the Examiner is respectfully requested in order to discuss the foregoing claims.

Except for issue fees payable under 37 C.F.R. 1.18, the Commissioner is hereby authorized by this paper to charge any additional fees during the entire pendency of this application, including fees due under 37 C.F.R. 1.16 and 1.17 which may be required, including any required extension of time fees, or credit any overpayment to Deposit Account 50-0310. This paragraph is intended to be a **constructive petition for extension of time** in accordance with 37 C.F.R. 1.136(a)(3).

Dated: **March 7, 2005**
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